UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/864,637	05/23/2001	Chia-Lin Wei	00801.0197.NPUS00	1716

25871 7590 02/25/2003

SWANSON & BRATSCHUN L.L.C.
1745 SHEA CENTER DRIVE
SUITE 330
HIGHLANDS RANCH, CO 80129

EXAMINER
STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 02/25/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/864,637	WEI ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *33-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4, 5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-14) in Paper No. 12 is acknowledged. The traversal is on the ground(s) that search for methods claimed in Groups II and III would not constitute undue burden on the examiner. This is found persuasive and Groups I-III (claims 1-32) will be examined together. Group IV (claim 33-36), drawn to normalized cDNA libraries, will not be rejoined with Groups I-III.

2. Claims 33-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

4. The disclosure is objected to because of the following informalities: on page 3, line 17 "... method of eualizing an cDNA library...".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 is indefinite over the recitation of the limitation "... there is a differential of the amount of labeled probe of said labeled probe library hybridized to each individual member of said non-normalized cDNA library..." (lines 10-12 of the claim; emphasis added). It is not clear how a differential of a probe amount can be labeled to a single member of the library.

B) The term "low amounts of labeled probe" in claim 1 is a relative term which renders the claim indefinite. The term " low amounts of labeled probe " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification does not contain a definition of what amount of labeled probe is considered "low".

C) Claim 10 is indefinite over the recitation of the limitation "... said constructing...". Claim 1, from which claim 10 depends, refers to "constructing a normalized cDNA library" in the preamble, "constructing a non-normalized cDNA library" in step (a) and "constructing a labeled probe library" in step (c). It is not clear which one of those constructing steps is referred to in this phrase.

D) Claim 14 is indefinite over the recitation of the limitation "... wherein said amplifying comprises growing each said host cell containing,...". It is not clear what the cells contain.

E) The term "library is represented in low amounts " in claim 15 (lines 10 and 26) is a relative term which renders the claim indefinite. The term " low amounts " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of

ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification does not contain a definition of what amount of a library is considered "low".

F) The term "library is represented in high amounts " in claim 15 (lines 12, 14, 23/24) is a relative term which renders the claim indefinite. The term " high amounts " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification does not contain a definition of what amount of a library is considered "high".

G) Claim 15 is indefinite over the recitation of the limitation "... said group of members..." in step (e). It is not clear what group of members this term refers to. In step (c), there is "... one group of members ... is represented in low amounts..." and "... one or more groups of members ... is represented in high amounts...". In step (d), there is "... selecting one group of said one or more groups of members...". Therefore it is not clear whether "said group of members" in step (e) refers to step (c) or (d).

H) Claim 15 is indefinite over the recitation of the limitation "... said group of members..." in step (f). It is not clear what group of members this term refers to. In step (c), there is "... one group of members ... is represented in low amounts..." and "... one or more groups of members ... is represented in high amounts...". In step (d), there is "... selecting one group of said one or more groups of members...". In step (e), there is "... identifying the members in said group of members...". Therefore it is not clear whether "said group of members" in step (f) refers to step (c), (d) or (e).

I) Claim 15 is indefinite over the recitation of the limitation "... said one or more groups of members..." in step (g). It is not clear what group of members this term refers to. In step (c), there is "... one or more groups of members...". In step (d), there is "... selecting one group of said one

or more groups of members...". Therefore it is not clear whether "said one or more groups of members" in step (g) refers to step (c) or (d).

J) Claim 15 is indefinite over the recitation of the limitation "... said group of members..." in step (h). It is not clear what group of members this term refers to. In step (c), there is "... one group of members ... is represented in low amounts..." and "... one or more groups of members ... is represented in high amounts...". In step (d), there is "... selecting one group of said one or more groups of members...". In step (e), there is "... identifying the members in said group of members...". In step (f), there is "... said group of members...". Therefore it is not clear whether "said group of members" in step (h) refers to step (c), (d) (e) or (f).

K) Claim 24 is indefinite over the recitation of the limitation "... said constructing...". Claim 15, from which claim 24 depends, refers to "constructing a normalized cDNA library" in the preamble and "constructing a non-normalized cDNA library" in step (a). It is not clear which one of those constructing steps is referred to in this phrase.

L) Claim 28 is indefinite over the recitation of the limitation "... wherein said amplifying comprises growing each said host cell containing,...". It is not clear what the cells contain.

M) The term "library represented in low amounts " in claim 31 (line 3) is a relative term which renders the claim indefinite. The term " low amounts " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification does not contain a definition of what amount of a library is considered "low".

N) Claim 31 is indefinite over the recitation of the limitation "... members that are represented by more than once;". It is not clear what this phrase means.

O) Claim 32 recites the limitation "said group of members" in line 9. There is insufficient antecedent basis for this limitation in the claim. There is no reference to "a group of members" elsewhere in the claim.

P) The term "library represented in low amounts " in claim 32 (line 10) is a relative term which renders the claim indefinite. The term " low amounts " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification does not contain a definition of what amount of a library is considered "low".

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-5, 7, 10, 11, 13, 14 and 32 rejected under 35 U.S.C. 102(b) as being anticipated by Nelson et al. (Genetic Analysis: Biomolecular Engineering, vol. 15, pp. 209-215, 1999; cited in the IDS).

Regarding claims 1 and 32, Nelson et al. teach construction of normalized cDNA library. First, a non-normalized cDNA library was constructed from polyA+ RNA isolated from normal human prostate tissue. Members of the library were separated by plating individual clones onto 384-well microtiter plates, grown and replica-spotted onto nylon membranes. The replicas were allowed to grow on the membranes, and then the colonies were lysed, providing DNA bound to the membrane (page 210, third paragraph). A labeled probe library was constructed by reverse transcription of the polyA+ RNA isolated from normal human prostate tissue using oligo-dT-30

primer, reverse transcriptase, dATP, dTTP, dCTP, dGTP and ^{32}P-dCTP, in a reaction at 42 °C for 30 minutes (page 210, fourth paragraph).

The filters were hybridized with the labeled probe, exposed to phosphor capture screens and the signals were quantitated on a phosphorimager. Clones with signal intensities within the bottom quartile of the averaged intensities were selected (page 210, fifth and sixth paragraphs). A total of 842 cDNA clones were selected based on low hybridization intensities, of which 142 were discarded. Of the remaining 700 cDNA clones, 89% of sequences were genes of low abundance (= low expression) (page 211, fourth and fifth paragraphs; Table 1).

Regarding claims 2-5 and 7, Nelson et al. teach isolation of polyA+ RNA from normal human prostate cells. Nelson et al. do not specifically say that the RNA was mRNA, but only mRNA in the eucaryotic cells is polyadenylated (page 210, third paragraph).

Regarding claims 10 and 11, Nelson et al. teach reverse transcription of the polyA+ RNA isolated from normal human prostate tissue using oligo-dT-30 primer, reverse transcriptase, dATP, dTTP, dCTP, dGTP and ^{32}P-dCTP, in a reaction at 42 °C for 30 minutes (page 210, fourth paragraph).

Regarding claim 13, Nelson et al. do not explicitly teach transformation of the members of non-normalized cDNA library into host cells, but since they do have clones, these could have been obtained only by transforming the library into host cells. See also Nelson et al. (Genomics, vol. 47, pp. 12-25, 1998; page 13, incorporated by reference).

Regarding claim 14, Nelson et al. teach growing host cells containing cDNA inserts on microtiter plates prior to hybridization (page 210, third paragraph).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. as applied to claims 1-5 above, and further in view of Somerville et al. (Science, vol. 285, p. 380-383, 1999).

A) Claim 6 is drawn to a plant cell being a soy, tobacco, wheat, rice or corn cell.

B) Nelson et al. teaches construction of normalized cDNA libraries from human prostate cells, but does not teach plant cells. However, Nelson et al. teach a method which is generally applicable to any type of cells and libraries constructed. Nelson et al. state that "...This procedure has several advantages over other methods such as normalization and subtraction for reducing the variation in abundance among the clones in a cDNA library. Standard library construction methods are employed without the necessity for PCR, reassociation reactions, or column purification of single-stranded DNA as used in several of the normalization and subtraction methods (citation omitted). Libraries previously made or purchased can be used without requiring new library construction." (page 214, second paragraph). In the Abstract, Nelson et al. point that "The identification of the entire complement of genes expressed in a cell, tissue or organism provides a framework for understanding biological properties and establishes a tool set for subsequent functional studies. The large-scale sequencing of randomly selected clones from cDNA libraries has been successfully employed as a method for identifying a large fraction of these expressed

genes. However, this approach is limited by the inherent redundancy of cellular transcripts reflecting widely variant levels of gene transcription. As a result, a high percentage of transcript duplications are encountered as the number of sequenced clones accrues."

C) Somerville et al. teach sequencing of Arabidopsis thaliana and rice genome. Rice was chose because of its similarities with wheat, maize and other cereals. They also teach that it is unlikely that other whole plant genomes would be sequenced because of the cost involved (page 380, third and fourth paragraphs).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have applied the library normalization method of Nelson et al. to rice and other plant genomes of Somerville et al. The motivation to do so, expressly provided by Nelson et al., would have been that library normalization permitted full elucidation of genes expressed in a given cell.

11. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. as applied to claims 1-5 and 7 above, and further in view of El-Meanawy et al. (Am. J. Physiol. Renal Physiol., vol. 279, p. F383-F392, 2000).

A) Claim 8 is drawn to a human cell being a kidney cell.

B) Nelson et al. teaches construction of normalized cDNA libraries from human prostate cells, but does not teach human kidney cells. However, Nelson et al. teach a method which is generally applicable to any type of cells and libraries constructed. Nelson et al. state that "...This procedure has several advantages over other methods such as normalization and subtraction for reducing the variation in abundance among the clones in a cDNA library. Standard library construction methods are employed without the necessity for PCR, reassociation reactions, or column purification of single-stranded DNA as used in several of

the normalization and subtraction methods (citation omitted). Libraries previously made or purchased can be used without requiring new library construction."

C) El-Meanawy et al. teach construction of mouse kidney expression libraries using the SAGE (serial analysis of gene expression) method. The library construction was the first step to analysis of gene expression in progressive kidney disease based on mouse model (Abstract, page F383). However, they point to the fact that SAGE does not provide reliable detection of transcripts with low abundance (page F390, second paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the library construction method of Nelson et al. to obtain clones from human kidney cell. The motivation to do so, expressly provided by El-Meanawy et al., would have been that expression libraries were a powerful tool to apply to elucidation of the mechanisms of renal disease because of the complexity of the disease and lack of effective treatments.

12. Claims 9 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. as applied to claim 1 above, and further in view of Frohman et al. (PNAS USA, vol. 85, pp. 8998-9002, 1988).

A) Claim 9 is drawn to the normalized cDNA library being a full-length cDNA library and claim 12 is drawn to the non-normalized cDNA library being a full-length cDNA library.

B) Nelson et al. do not teach either the normalized or non-normalized libraries being full-length cDNA libraries.

C) Frohman et al. teach a method (RACE) for obtaining full-length cDNA clones of low abundance mRNAs. The method involves amplification of 3' and 5' ends of cDNAs, followed by assembly of the fragments into a full-length cDNAs, which can then be cloned (Figure 1; page 8999, the last paragraph; page 9000).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the libraries of full-length cDNAs of Frohman et al. in the method of library construction of Nelson et al. The motivation to do so would have been that using full-length cDNAs accelerated processes of gene characterization and protein expression.

13. No references were found teaching or suggesting claims 15-31, but they are rejected for reasons given above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

February 24, 2003

Teresa Strzelecka

Patent Examiner

Teresa Strzelecka
2/24/03